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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/049,865	03/27/1998	COLLIN J. WEBER	47765/C/JPW/	6162

7590 03/17/2004

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EXAMINER	
DAVIS, MINH TAM B	

ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 03/17/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Advisory Action	Application No.	Applicant(s)	
	09/049,865	WEBER ET AL.	
	Examiner	Art Unit	
	MINH-TAM DAVIS	1642	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 21 November 2003 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE. Therefore, further action by the applicant is required to avoid abandonment of this application. A proper reply to a final rejection under 37 CFR 1.113 may only be either: (1) a timely filed amendment which places the application in condition for allowance; (2) a timely filed Notice of Appeal (with appeal fee); or (3) a timely filed Request for Continued Examination (RCE) in compliance with 37 CFR 1.114.

PERIOD FOR REPLY [check either a) or b)]

a) ☒ The period for reply expires 6 months from the mailing date of the final rejection.

b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection. ONLY CHECK THIS BOX WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

1.☒ A Notice of Appeal was filed on *14 January 2004*. Appellant's Brief must be filed within the period set forth in 37 CFR 1.192(a), or any extension thereof (37 CFR 1.191(d)), to avoid dismissal of the appeal.

2.☐ The proposed amendment(s) will not be entered because:

(a) ☐ they raise new issues that would require further consideration and/or search (see NOTE below);

(b) ☐ they raise the issue of new matter (see Note below);

(c) ☐ they are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or

(d) ☐ they present additional claims without canceling a corresponding number of finally rejected claims.

NOTE: _____.

3.☐ Applicant's reply has overcome the following rejection(s): _____.

4.☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).

5.☒ The a)☐ affidavit, b)☐ exhibit, or c)☒ request for reconsideration has been considered but does NOT place the application in condition for allowance because: *see attached*.

6.☐ The affidavit or exhibit will NOT be considered because it is not directed SOLELY to issues which were newly raised by the Examiner in the final rejection.

7.☒ For purposes of Appeal, the proposed amendment(s) a)☐ will not be entered or b)☒ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.

The status of the claim(s) is (or will be) as follows:

Claim(s) allowed: *NONE*.

Claim(s) objected to: *NONE*.

Claim(s) rejected: *54-59 and 62-70*.

Claim(s) withdrawn from consideration: _____.

8.☐ The drawing correction filed on _____ is a)☐ approved or b)☐ disapproved by the Examiner.

9.☐ Note the attached Information Disclosure Statement(s)(PTO-1449) Paper No(s). _____.

10.☒ Other: *attached signed PTO-1449 of 03/04/02*

DETAILED ACTION

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Accordingly, claims 54—59, 62-70 are being examined.

The following are the remaining rejections.

INFORMATION DISCLOSURE STATEMENT

The reference of the information disclosure statement of 03/04/02 has been reviewed, and a signed PTO-1449 is enclosed hereto.

REJECTION UNDER 35 USC 112, FIRST PARAGRAPH, SCOPE

Rejection under 35 USC 112, first paragraph, pertaining to lack of enablement for "any agent" that inhibits an immune system costimulation event remains for reasons already of record in paper No.21.

Applicant argues as follows:

Applicants rely on the high level of skill in the art, the working examples the specification, and particularity of the event itself, which necessarily limits the range of possible inhibitors.

As defined the specification page an "immune-system costimulation event" is an interaction between an APC and a T-cell, including any specific binding cell-surface molecule, other than an MHC-bound antigen, to specific ligand T-cell. As further taught in the specification and the prior art, the APC:T-cell interaction that results in the

costimulation event between the B7 molecule on the APC and either CD28 or CTLA4 on the T-cells. Specific examples inhibitors this interaction were known in the art and are described specification, B7 monoclonal antibodies (Lenschow p.790), CTLAMIg, CD28Ig, and B7Ig (Linsely at col. 14, 17).

Applicant's arguments set forth in paper of 11/21/03 have been considered but are not deemed to be persuasive for the following reasons:

Contrary to Applicant's assertion, the range of possible inhibitors is not limited, but encompass a whole universe of inhibitors having any structure, such as small molecule inhibitors, mimetics of B7 or CTLA4 or CD28, or analogs of B7 or CTLA4 or CD28, as defined in the specification. Applicant has not taught how to make these molecules for use in the claimed method.

REJECTION UNDER 35 USC 103

Claims 54-59, 62-70 remain rejected under 35 USC 103, pertaining to obviousness over Lenschow et al, in view of Goosen et al, Soon-Shiong et al, Akalin et al, Linsley et al, Padrid et al, and Steurer et al for reasons already of record in paper No.11.

Applicant argues as follows:

Applicant asserts that the Examiner relies upon his view of the knowledge generally available to one of ordinary skill in the art to provide both the suggestion and motivation to combine the teaching of the references, as well as the expectation of

success in making said combination. Applicant asserts that the Examiner's reasoning is based on impermissible hindsight and "an obvious to try" rationals.

Applicants maintain that the Examiner ignores the high degree of uncertainty in the art at the time of filing with respect to the cause of graft destruction where microencapsulation prevented contact between host effector cells and graft cells. The specification teaches this uncertainty regarding the mechanism of encapsulated graft destruction beginning at page 8. A number of theories that had been posited in the prior art are set forth therein. For example, cytotoxic factors were posited to permeate the capsule membrane, causing graft destruction. Such factors were known to be produced by host immune cells such as natural killer cells, cytotoxic T-lymphocytes, and macrophages (Soon-shiong at 218, and the specification at page 8, lines 23-32). Another possibile source of cytotoxic factors was from xenogeneic macrophages within the graft itself (see page 9, lines 14-34). Finally, the specification teaches that T-helper cells were suspected in the rejection of encapsulated grafts (see page 9, lines 1-12). However, absent the teachings of the instant disclosure, the prior art provides nothing more than a general approach toward what seemed like a promising direction, i.e., inhibition of APC:T-cell interaction, among a number of other, equally promising directions, i.e., inhibition of toxin release by natural killer cells, cytotoxic T-lymphocytes, and macrophages, or improvements in capsule design to protect the graft from such cytotoxic factors.

Applicants further submit that the prior art teaches away from combining CTLA4Ig with microencapsulation. Although Lenschow demonstrates improved

xenogeneic graft survival by treatment with CTLA4Ig, Lenschow strongly supports the view that the immune response to the graft involves direct presentation of xenogeneic antigens by graft APCS (Lenschow at 790-91). In other words, following the teachings of Lenschow, the artisan would be motivated to inhibit the interaction between host T-helper cells and graft APCS. Since this is accomplished by the physical barrier of the microcapsule itself, there is no reason to also administer CTLA4Ig where the graft is encapsulated. Moreover, while acknowledging the possilility that host B7+APCs might be involved in xenograft rejection, Lenschow proceeds to teach away from this possibility by offering .another explanation f or the inability of the anti-B7/ MAb to block rejection as effectively as CTLA4 Ig, namely, inadequate antibody dosage (Lenschow at 791) .

Applicant's arguments set forth in paper of 11/21/03 have been considered but are not deemed to be persuasive for the following reasons:

Lenschow et al teach that control animal demonstrates evidence of immune rejection, with a marked lymphocytic infiltrate into the graft and that transplant tissue from mice treated with CTLA4Ig, which target T cells, is devoid of any lymphocytic infiltrate (p.790, last column, first para). Thus from the teaching of Lenschow et al one would have expected that the graft rejection is due to infiltration of lymphocytes. This is confirmed by the teaching of Soon-Shiong et al, who teach that microencapsulation of isolated islets prevents graft rejection, by protecting the transplanted cells from both cytotoxic T-lymphocytes and natural killer cells.

Further, it is not germane whether cytotoxic factors produced by natural killer cells, cytotoxic T-lymphocytes and macrophages could or could not permeate the capsule membrane, because one would have expected that problems due to the presence of cytotoxic T-lymphocytes and natural killer cells could be prevented by microencapsulation of isolated islets, in view of the teaching of Soon-Shiong et al that microencapsulation of isolated islets prevents graft rejection, by protecting the transplanted cells from both cytotoxic T-lymphocytes and natural killer cells, and further in view of the teaching of Goosen et al that microcapsules encapsulating islets of Langerhans is impermeable to immune system proteins. Concerning whether T-helper cells were suspected in the rejection of encapsulated grafts, one would have expected that T helper cells could not enter the microcapsules, which is impermeable to even smaller compounds, such as immune system proteins, as taught by Goosen et al. Thus one would have expected that using microcapsules would obviate these possible causes of graft destruction, if they exist, and certainly would be complementary to CTLA4Ig in protecting the graft from cells of the immune system, such as T cells and natural killer cells, and immune system proteins.

Moreover, contrary to Applicant's arguments, Lenschow et al do not teach away from the invention. The teaching of Lenschow et al that it is not certain whether the host or graft APCs are also involved in graft rejection is not germane, in view of that graft rejection is due to the presence of lymphocytes, such as T lymphocytes, as taught by Lenshow et al, and Soon-Shiong et al, and not due solely to APCs, wherein rejection due to lymphocytes clearly could be prevented by microcapsulation of the graft as

taught by Soon-Shiong et al. Further, it is noted that in view that microencapsulation of isolated islets alone prevents graft rejection, as taught by Soon-Shiong et al, one would have expected any graft APCs damage to the islets within the microcapsules would not be significant.

Thus the motivation for combining the references flow naturally from the teaching in the art, i.e. microencapsulation of the islet cells would be complementary to CTLA4Ig, because both prevent graft rejection, but by different mechanisms, and thus a combination of microencapsulation of the islet cells and CTLA4Ig would increase the chance of preventing graft rejection by the immune system.

One would have a reasonable expectation of a success of preventing graft rejection, because both microencapsulation of the islet cells and CTLA4Ig could prevent graft rejection, but by different mechanisms.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MINH-TAM DAVIS whose telephone number is 571-272-0830. The examiner can normally be reached on 9:30AM-4:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, YVONNE EYLER can be reached on 571-272-0871. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

MINH TAM DAVIS
March 09, 2004

SUSAN UNGAR, PH.D
PRIMARY EXAMINER